

Improvement of Quality of Life in Tumor Patients after an Immunomodulatory Treatment with Standardized Mistletoe Lectin and Arabinoside Plant Extracts

Tibor Hajto*, Anna Horváth and Szidonia Papp

Institute of Pharmaceutical Chemistry, Medical University Pécs, Hungary

*Corresponding author: Tibor Hajto, Institute of Pharmaceutical Chemistry, Medical University Pécs, Hungary, Tel: +36 309 735 337; E-mail: drhajtot@t-online.hu

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Abstract

Background: In the last decades a special attention has been focused on the role of disturbed immune balance in the behavioral co-morbidities of tumor patients. The prognostic significance of malignant tumor-induced imbalance in the innate immune system is well known. The innate system uses a limited number of Pattern Recognition Receptors (PRR) to recognize conserved Pathogen Associated Molecular Pattern (PAMP) structures expressed by microbes but not by host. Growing experiences suggest that the improvement of tumor induced disturbance of immune balance by using standardized plant PAMP like preparations goes often together with a better quality of life (QoL).

Methods: In this study tumor patients were treated with standardized plant immunomodulators (mistletoe lectin and arabinoside) which were shown to activate the type-1 natural immune cells against cancer. After at least a therapy for six months the patients were asked about their QoL using questionnaires.

Results: The following answers were received from the 35 patients: Decrease of pains: 17%, improvement of anxiety: 40%, Increase of physical activity: 71%, Improvement of appetite: 66%, Improvement of sleep: 40%, improvement of digestion: 43%, decrease of side effects during oncotherapy: 71%, beneficial judgement of the progress of disease based on clinical findings: 46%. As shown, the most important effects were the improvement of physical activity and decrease of side effects during conventional oncotherapy.

Conclusion: Present results may support the relationship between tumor induced disturbance of immune balance and the tumor induced behavioral co-morbidities. Further clinical investigations are necessary to proof this hypothesis.

Keywords: Quality of life; Immunomodulatory treatment; Tumor disease; Mistletoe lectin; Arabinoside

function of Natural Killer (NK) cells which are important part of type-1 innate immune system with antitumor properties [5-8].

Introduction

There is a rich literature describing potential consequences of behavioral co-morbidities in patients with cancer. The impaired quality of life (QoL) appears to be correlated with increased disease-related morbidity and mortality, and can also reduce treatment adherence [1,2]. The most often observed behavioral alterations of patients with cancer include fatigue, depression, and cognitive dysfunction [2]. Fatigue is commonly reported by cancer patients with a prevalence of nearly 80% in some tumor types [3]. Cancer-related fatigue occurs most often after surgery, chemotherapy, or radiotherapy and it has been reported by cancer patients to be the major obstacle for normal cognitive functions and a good QoL [3]. In addition, fatigue can also increase the cancer-related pains [4]. Little is known about the effect of immunomodulatory treatments on the behavioral co-morbidities of patients with cancer but growing experiences suggest that an improvement of cancer-related disturbance in immune balance by using immunomodulators is often beneficial. In this paper these connections are analyzed using data originated from questionnaires of tumor patients who were treated with standardized plant immunomodulators. Standardized mistletoe lectin and arabinoside plant extracts were shown to activate phagocytic activity and the

Material and Methods

Mistletoe extract standardized by the determination of its mistletoe lectin level

Iscador^R is a fermented aqueous mistletoe plant extract manufactured and supplied by Iscador AG (CH-4144 Arlesheim, Switzerland). The active (sugar-binding) lectin content of commercially available mistletoe extracts (IscadorR M spec 5 mg) was measured in the research laboratory of Pharmaceutical Chemistry Department of Medical University Pécs.

The determination of sugar binding mistletoe lectin (ML) level in extracts was carried out by an optimized ELLA technique as published previously [9].

Standardized ME exhibited a bell-shaped dose-response relationship and 0.5- 1.0 ng/kg lectin doses were found to be most effective as it was always assessed previously using healthy volunteers. Since two and three therapy-free days were found to be necessary for an immunologically optimal effect, the subcutaneous ME injections were regularly given twice a week.

Standardized rice bran extract (BioBran/MGN-3)

The second immunomodulatory drug used in the combinative treatment of the presented patients is BioBran/MGN-3 which is manufactured and supplied by Daiwa Pharmaceutical Co, Ltd, Tokyo, Japan. BioBran/MGN-3 is composed of denaturated hemicellulose, which is obtained by rice bran hemicellulose reacting with multiple carbohydrate-hydrolyzing enzymes from shiitake mushrooms. BioBran/MGN-3 is standardized for its main chemical component: arabinoxylan with a xylose (in its main chain) and with an arabinose polymer (in its side chain). To the presented patients BioBran/MGN-3 was given orally in doses between 12 and 45 mg/kg twice a week parallel to the optimized, lectin-oriented mistletoe extract therapy.

Patients

Using questionnaires 35 answers were received from the patients: 20 females and 15 males, the average age was 63, 9 (17-79) years, they had mostly advanced (II-IV) stages of their tumor disease. They must be suitable for the inclusion criteria: they had histological proved malignant tumor, no morphine preparation was applied, and they were treated at least or longer than 6 months with standardized Arabinoxylan (BioBran) and standardized mistletoe lectin preparations (Iscador M 5 mg). The diagnosis of patients is shown in the Table 1. In the questionnaires sent to tumor patients eight questions were ranged in yes/no type as shown in Table 2.

Breast cancer	6
Colon cancer	4
Uterus cancer	3
Prostata carcinoma	3
Lung planocellular carcinoma	2
Lung adenocarcinoma	2
Renal cell carcinoma	2
Malignant melanoma	2
Stomach cancer	2
Sarcoma	2
Ovarian cancer	1
Basalioma	1
Small cell lung cancer	1

Table 1: The questionnaires of 35 tumor patients (20 females and 15 males) were evaluated. They had mostly advanced (II-IV) stages of their tumor disease. The distribution of their diagnosis is discussed.

1	Decrease of pain	Yes or not
2	Decrease of anxiety	Yes or not
3	Increase of physical activity	Yes or not
4	Improvement of appetite	Yes or not
5	Improvement of sleep	Yes or not
6	Improvement of digestion	Yes or not
7	Decrease of side effects during the conventional oncologic therapy	Yes or not
8	How did you judge the advance of your tumor disease based on clinical evidence and control investigations?	Positive or negative

Table 2: Questionnaires sent to patients who all had histological improved malignant tumor, no morphine preparations have received and they were treated longer than 6 months with standardized plant immunomodulators. The patients were asked to answer above questions.

Results

As shown in Figure 1, from the 35 patients the following answers were received: 1. Decrease of pains: 6 (17%), 2. Improvement of anxiety: 14 (40%), 3. Physical activity: 25 (71%), 4. Improvement of appetite: 23 (66%), 5. Improvement of sleep: 14 (40%), 6. Improvement of digestion: 15 (43%), 7. Only 24 patients of 35 were treated parallel with various oncologic treatments. 70, 8% (17) related a decrease of side effects during oncotherapy: 17; 8. Beneficial judgement of the progress of disease based on clinical findings: 16 (46%). The most important effects were the improvement of physical activity (71%) and appetite (66%).

Discussion

A great number of experimental data suggest that immune and neuroendocrine systems are not isolated from each other. They represent a very complex network. Clinical experiences suggest that a

therapeutic modulation of the immune system may induce beneficial effects on nerve system. Present results established a reduction of pains and anxiety as well as an increase in physical activity at tumor patients with advanced disease.

It is in agreement with previous experimental data of other authors, who have observed an immunomodulator-induced increase in the production of endogenous opiates and a correlation between immunomodulatory effects and beta-endorphin release was found [10,11].

Therefore the present results can support these observations and the beneficial effect of plant immunomodulators on the fatigue syndrome, appetite and anxiety are noteworthy.

In addition, we can't leave it out of consideration that 24 patients of 35, who were treated parallel with conventional oncologic therapy, 17 (71%) reported about an improvement of side effects. It is clear that a comparative study using placebo control would present these results

much better, but it was not possible to find appropriate match pair control persons.

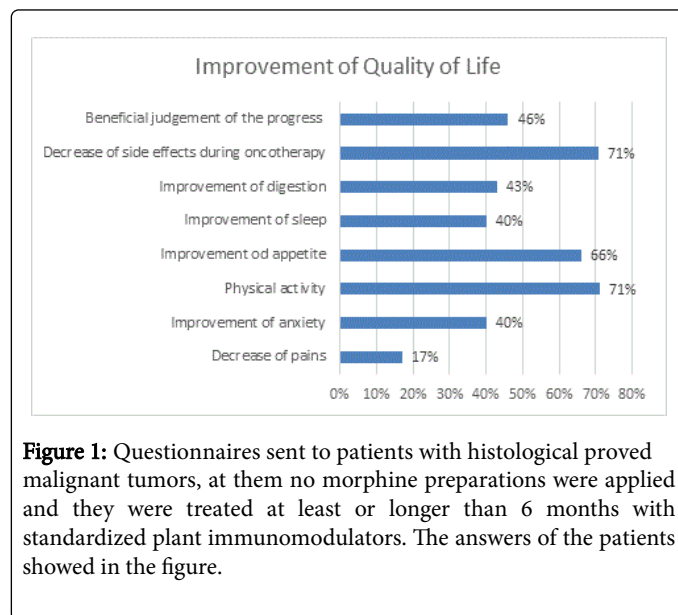


Figure 1: Questionnaires sent to patients with histological proved malignant tumors, at them no morphine preparations were applied and they were treated at least or longer than 6 months with standardized plant immunomodulators. The answers of the patients showed in the figure.

Special attention has been focused on the role of immunological processes in the impaired QoL of cancer patients. Behavioral comorbidities in cancer patients were found to be associated with decreased activity of phagocytes and natural killer cells [2] inducing a shift in the balance of Th1 and Th2 immune responses and an elevated activity of regulatory T cells [12]. Growing evidence suggests that mistletoe lectin (ML) has a great similarity to pathogens associated molecular pattern (PAMP) molecules of microorganisms. The immunomodulatory effect of mistletoe extract (ME) therapy is based on lectin – sugar interactions on cell membrane of innate immune system [5-6,13-15]. As known, the natural immune cells, such as granulocytes, macrophages, dendritic cells and natural killer (NK) cells, are able to enhance their basic activity against infections and tumor cells, if their appropriate pattern recognition receptors (PRR) are bound by PAMP ligands. It was found that ML molecules functioning as ligands for pattern recognition receptors of innate immune system and they are docked to appropriate ganglioside molecules (CD75) of natural immune cells [15]. Thereby ML is capable of having a positive effect on the disturbed immune balance of tumor patients and case reports show some clinical benefits [16-18]. The active (sugar-binding) lectin content of commercially available Iscador M special preparations is regularly measured by an optimized ELLA technique as published previously [9]. Arabinosyl concentrate (MGN3/BioBran) was found to have a synergistic effect on ML-induced immunomodulation [18]. Therefore the question arises as to whether an activation of type-1 natural immune cells can improve the QoL? Present clinical data may support this hypothesis.

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